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(WO/2001/008682) USE OF FLUPIRTINE FOR ALLEVIATING PAIN CAUSED BY DEGENERATIVE JOINT OF DISEASES IN DOGS AND CATS

Classification

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the Cauda equina syndrome belongs. With the latter it concerns the so-called "horse tail syndrome", by which dogs of large races (like shepherd dog) are affected predominantly. A cause of the pain are in the narrowing of the spinal column channel by the partial incident of the knorpeligen spinal column disk.

Also with the instability in the Lumbosakralengelenk pain arises, a whose cause is to be explained by volume stretch.

In the treatment of the chronic pain medicines with different damage mechanisms are used.

Thus also Corticosteroide, which release according to their damage mechanism also with animals serious side effects, are used.

Most frequently however not steriodale Entzündungshemmer (non steroidal anti- inflammatory drugs = NSAIDs) and so-called cartilage-protecting protektive (chondroprotektive) medicines are used.

To the knorpelprotektiven substances polysulfatiertes Glycosaminglykan and the combination of Chondroitin and Glukosamin belong. Polysulfatiertes Glycosaminglykan is given intramuskulär or intraartikulär (directly in the joint inside).

The effectiveness of this mixture is disputed not only in the humanmedical but also in the veterinary literature (deal, CL, RW Moskowitz.

Nutraceuticals as therapeutic agents in osteoarthritis. - The role OF glucosamine, chondroitin sulfates, and collagen hydrolysates. Rheumatism TIC Disease Clinics OF North America 25: 379-782,1999; DeHaan, JJ, Goring, RL, BS Beale and in evaluation OF polysulfated glycosaminoglycan for the treatment OF hip dysplasia in dogs. Vet.

Surg. 23: 177-181,1994).

Chondroitin and Glukosamin are orally used either as mono substance (Glukosamin) or in combination . Their effectiveness is occupied until today in no controlled clinical study both with humans and with animals (Leffler, CT, AF Philippi, SG Leffler, JC Mosure, PD Kim. Glucosamine, chondroitin, and magnesium ascorbate for degenerative joint disease OF the knee or low bake: A randomized, double-blindly, placebo control LED pilot study. Military medicine 164: 85-91,1999).

Even if under effects favorable in vitro conditions therapeutically seen shows the knorpelprotektiven substances, these effects were not placed under therapeutic conditions (in vivo) under proof.

(Bassler, C, L Rovati, P Franchimont. Stimulation OF proteoglycan production by glucosamine sulfates into chondrocytes isolated from humanly osteoarthritic articular cartilage in vitro. Osteoarthritis & Cartilage 6: 427-434,1998).

At this time there is no medicine, which could prevent the Destruktion of the cartilage.

In the future the destructive procedures are treated with such substances, which are causally involved in the pathogenesis of the Osteoarthrose and thus can stop progressing the Destruktion of the cartilage and the bone.

Numerous experimental investigations point out that TNFa (tumor necrosis factor a) a central role in the emergence of the degenerative joint changes plays. Osteoarthrose always accompanies with Destruktion of the cartilage and the bone . In the Osteoarthrose walk increased neutrophilen Granulozyten into the joint, which sets TNFa free. Further an increased formation of new containers under the influence of TNFa takes place .

Due to its growth becomes knorpel-bzw. bone-damaging fabric promoted (Paleolog, E. target effector role OF vascular

endothelium into the inflammatory response: insights from the clinical trial OF anti- TNFa antibody in rheumatoid arthritis. Mol. Pathol. 50: 225-233,1997). In clinical studies clearly it was proven that neutralization of TNFa either through against TNFa arranged monoclonal antibodies (anti- TNF mABs) or by use of loslichen TNFa receptors (soluble TNF receptor fusion of protein: STNFR IgGs) not only the acute symptoms (e.g.) But also always progressing Knorpel-und Knochendestruktion to be suppressed know joint swelling (Fenner, H. Immunpharmakologi profile and therapeutic perspectives of anti- TNFa therapies. Magazine. Rheumatol.

57: 294-297,1998; Moreland, L.W. Soluble tumor necrosis factor receptor (p75) fusion protein (Enbrel) as A therapy for rheumatoid arthritis. Rheum Dis. Clin. N.A.

24: 579-591,1998). Therefore it is quite conceivable that the training destructive Knorpel-und bone changes could be prevented by the employment by anti- TNF mABs and sTNFR IgGs .

In the veterinary medicine for the treatment by chronic pain NSAIDs are ordered predominantly. At present here in particular the following active substances are used: Aspirin, Carprofen, Ketoprofen, Piroxicam, Naproxen and Meclofenamic (Papich, G.M., Hardie E.M., management OF chronic pain).

There are however numerous references on it that those not steroidalen Entzündungshemmer the pain to alleviate are able, however the Knorpeldestruktion rather promotes (Wang, B, Yao, Y-Y, Chen M-Z. Effects OF indometacin on joint damage in advice and rabbit. Acta Pharmacol Sinica 19: 70-73, 1998; Rainsford, KD, Ying, C, Smith FC. Effects OF meloxicam, compared with other NSAIDs, on cartilage proteoglycan metabolism, synovial prostaglandin E2, and production OF interleukins 1.6 and 8 explants in organ culture porcine in humanly and. J. Farm. Pharmacol. 49: 991-8,1997; van the mountain, stock. Impact OF NSAID and steroids on cartilage destruction into murine antigen induced arthritis, J.

Rheumatol. 27 (Suppl.): 122-3,1991 ; Brandt, KD, Slowman Kovacs, S.

Nonsteroidal antiinflammatory drugs in treatment OF osteoarthritis. Clin.

Orthopaed. Relat. Dis. 213: 84-91,1986 ; Palmowski, MJ, KD Brandt. Aspirin aggravates the degeneration OF canine joint cartilage caused by immobilization.

Arthritis Rheum. 25: 1333-1342,1982).

As well known NSAIDs cause an increase of Leukotrienen , which are able to promote the degenerative processes as restrictors of the Cyclooxyeganase by shift of the Arachidonsäure metabolism (Brune, K, Aehringhaus, U, Peskar, B.A. Pharmacological control OF leukotriene and prostaglandin production from mouse peritoneal macro-far, Agents of act ion 14: 729-34,1984; Achterrath Tuckermann, And, Th. Simmet, W. Luck, I. Szelenyi, B.

A. Peskar. Inhibition OF cysteinyl leukotriene production by azelastine and its biological significance. Agents of act ion 24: 217-223 (1988).

In addition NSAIDs of serious gastrointestinal and other perhaps life-threatening side effects are afflicted (Forsyth, SF, Guilford, WG, Haslett, SJ, Godfrey, J. Endoscopy OF the gastrduodenal mucosa after carprofene, meloxicam and ketoprofen administration in dogs. J. Small Animal Practice 39: 421-4,1998).

In the past years two Subtypen of Cyclooxygenasen (COX) were discovered: COX-1 and COX-2. To be kept upright the COX-1-Enzym is a so-called " house keeping" enzyme, whose task it among other things is , for the protection of the gastrointestinal Mukosa as well as for the maintenance of the necessary renalen blood circulation to be ensured and a sufficient blood circulation .

In contrast to this the COX-2-Enzym is induced only by different factors and is responsible for the inflammatory procedures.

After all well-known NSAIDs does not exhibit therapeutic-relevant selectivity for COX-2, but almost directly strongly one restrains, does not need both enzymes not to be surprised that also with in more recent time the introduced NSAIDs gastrointestinal side effects arise.

Selective COX-2-Inhibitoren, which does not restrain the so-called "house keeping " enzyme COX-1 and thus the pro day land in synthesis in the gastrointestinal tract, does not lead to gastrointestinal damages.

NSAIDs such as acetylsalicylic acid, Ibuprofen, Ketoprofen, Naproxen, Carprofene, Diclofenac, Meclofenamsäure, Piroxicam, Meloxicam are however no selective COX-2-Hemmer.

Unite according to investigations are Meloxicam COX-2 selectively inhibieren (Churchill, L, AG Graham, CK Shih. Selective inhibition OF humanly cyclo oxygenase-2 by meloxicam. Inflammopharmacol. 4: 125-135,1996).

Against this selectivity however the clinical results, there also with the use of Meloxicam the typical NSA-ID-caused incompatibility reactions , speak like gastrointestinal and renale disturbances arise (Committe on Safety OF Medicine/Medicines control Agency. Meloxicam (Mobic): gastrointestinal and skin reactions. Current of problem of 24: 13,1998; Gaßner, G, I Stefan, I Schutt-Mast. Observations to side effects after use of nichtsteroidalen Antiphlogistika with the dog. Veterinary surgeon. Pax.

26 (K): 119-123,1998).

Other NSAIDs, like Carprofene restrains the two Subtypen of COX with same effect strength (Vane, JR, RM Bottin. New insights into the fashion OF action OF anti inflammatory drugs. Inflamm. Res. 44: 1-10,1995).

Therefore quite gastrointestinal side effects can occur with application of such NSAIDs (Forsyth, SF, WG Guilford, SJ Haslett, J Godfrey.

Endoscopy OF the gastroduodenal mucosa after carprofene, meloxicam and ketoprofen administration in dogs. J. Small Animal Pract. 39: 421-424,1998; Tjalve, H. Adverse reactions tons veterinary drugs reported in Sweden during 1991 - 1995. J. Vet. Pharmacol. Therap. 20: 105-10,1997)).

In case of of Carprofene it was necessary, the data for possible side effects to that extent too changes that also to possible gastrointestinal Unverträglichkeiten (bleeding, Ulkusbildung) it must be referred. Also a possible impairment of the renalen function, which is a typical side effect of NSAIDs, had to be mentioned in the new enclosing note by Carprofene (Veterinary reporting results in product labeling CHANGE, USP quality Review No.

63, May 1998).

With many analgesics also different unwanted reactions can occur apart from the classical gastrointestinal and renalen side effects, which are not to be explained COX with the inhibition of the enzyme. They are substance specific and arise with certain medicines. Thus for example with Diclofenac, Naproxen, Nimesuli and Piroxicam occasionally liver damage was observed (Helfgott SM, et al. Diclofenac associated hepatotoxicity. JAMA 264: 2660-2662,1990; Andrejak, M, et al. CROSSes hepatotoxicity between non steroidal anti- inflammatory drugs. Br. Med. J.

295: 180-181,1987 ; McCormick, Pa, et al. COX-2 inhibitor and fulminant hepatic failure, Lancet 353: 40-41,1990; Paterson D, et

al . Piroxicam induced submassive necrosis OF the more liver. Well 33: 1456-1458,1992).

Also with the Arylpropionsaure derivative Carprofene was reported on Hepatotoxizität, whereby also causality could be proven, since after setting the carprofene therapy off with most dogs a complete normalization of the liver values entered (MacPhail, cm, MR Lappin, DJ Meyer, SG Smith, CRL Webster, PJ Armstrong. Hepatocellular toxicosis associated with administration OF carprofene in 21 dogs. JVMA 212 : 1895-1901, 1998).

Due to these findings also this not COX specific side effect had to be taken up to the new enclosing note for Carprofene (Veterinary reporting results in product labeling CHANGE, USP quality Review No. 63, May 1998).

Many NSAIDs are razemische mixtures. With exception of Naproxen all Arylpropionsäure derivatives are such mixtures that is called in the commercially available formulations are both R-as also S the isomer available. Pharmakologisch therapeutically effectively are however only the S-isomers.

In the organism however both isomers will have amplifier-off-changed and both isomers from the body to be removed. This additional Metabolisierung and elimination of the pharmacodynamically inactive isomer represent a substantial load for the organism.

With the therapeutic use of razemischen mixtures the organism is loaded with 50% ballast materials. Further the inactive isomers can contribute perhaps also to the drug interactions (Szelenyi, I, G Geisslinger, E Polymeropoulos, W Paul, M Herbst, K Brune. The material Gordian knot: Racemic mixtures versus pure enantiomers. Drug news & Perspectives 11: 139-160,1998).

It is also well-known that NSAIDs, like Diclofenac, are incomparably better compatible Aspirin in the human therapy than with dogs. Investigations showed that treatments had to be broken off by dogs with Diclofenac, since indisposition and vomiting arose (Wigger, among other things, plasma and tissue kinetics OF diclofenac into the dog; Arch Pharmacol ; 357; No. 4, Supol; R5, 1998).

A ever greater importance is attached to the pain treatment as well as prevention of a Schmerzchronifizierung with degenerative joint illnesses of dogs and cats. in particular here the side effect potential must be small apart from a good analgetischen effectiveness of the assigned active substance.

The appropriate pharmaceutical preparations must be present here in and a geschmacklich well compatible form easily einnehmbaren for dogs and cats.

It was found surprising now that Flupirtin or its can be used pharmaceutical compatible salts for the treatment by pain as well as prevention of a Schmerzchronifizierung with degenerative joint illnesses with dogs and cats with small side effect potential.

Flupirtin was not used so far yet in the veterinary medicine.

Flupirtin is a Triaminopyridin derivative with the chemical designation 2-Amino 3-ethoxycarbonyl-amino-6 (p-fluorine-benzylamino) - pyridin.

It is a central working analgesic, however without craze potential and also without side effects typical for other central analgesics such as blockage, breath depression, tolerance development and withdrawal symptoms.

From the literature it is well-known that Flupirtin can be used in the human therapy for the treatment of different illnesses.

Thus Flupirtin has muskelrelaxierende characteristics, so that Flupirtin can be used also for the treatment by muscle spannings or when illnesses, which are based on muscle spannings, (DE 40 22 442, US 5,152,346, US 5,284,861).

Further on investigations of the muskelrelaxierenden effect of Flupirtin at the rat it was found that the Flupirtin is suitable also for the treatment by NMDA obtained ZNS illnesses, like for example cerebral Ischämie, neurodegenerative illnesses and epilepsy (DE 43 27 516, US 5,721,258).

In WHERE 97/17072 the use from Flupirtin to the treatment of illnesses of the hämatopoetischen cell system, like AIDS pointed out.

Likewise it could be proven that Flupirtin can be used for the treatment by illnesses, which accompany with a unphysiologisch high cell mortality rate (WHERE 97/49398).

The synthesis of Flupirtin and its pharmaceutical usable salts is described in the patents DE 17 95 858, DE 31 33 519 and DE 34 16 609.

Regarding the damage mechanism of Flupirtin there are several mechanisms, its analgetische effect erkl eras : 1) Flupirtin activates the noradrenergen descending courses in back Mark (nickel, B, angel, J, Szelenyi, Ith Possible OF involvement noradrenergic descending pain modulating pathways into the fashion OF antinociceptive action OF flupirtine, A novel non opioid analgesic. Agents of act ion 23: 112-116,1988; Szelenyi, I., nickel, B., Borbe, HO, Brune, K. mode OF action OF flupirtine into the advice.

Br. J. Pharmacol. 97: 835-842,1989).

2) Flupirtin strengthens the antinociceptiven GABAerge mechanisms (wiser, T, Wienrich M, Szelenyi, Ith The amplification OF the GABAA response by flupirtine is mediated via the steroid being thing site. Arch. Pharmacol. 349 (Suppl.): R 383.1994) 3) in the literature gives it numerous references on the fact that the opening of the ATP sensitiven K+-channels to the analgetischen effect leads (Asano, T, Iida, H, Dohi, S, Masue, T, Shimonaka, H. Nicorandil, as ATP sensitive K+ channel more opener, potentiated morphines analgesie. Jap. J. Anesth. 45: 1342-1346,1996; Robles, left, Barrios M, Del Pozo E, Dordal, A, Baeyens, JM. Effects OF K+ channel blocker and openers on antinociception induced by agonists OF 5-HT1A receptors. Eur. J.

Pharmacol. 295: 181-188,1996).

Own investigations point to that the active substance Flupirtin opens certain K+-channels and over this way its analgetische effect unfolded.

4) According to newest investigations Flupirtin opens also the so-called tension-independent K+-channels in the central nervous system.

Due to this damage mechanism Flupirtin is also able to prevent the Chronifizierung of hurting (Kornhuber, J. a pain killer, which differs from all well-known analgesics. Med. week 64: 10, 1999). With high probability the analgetische effect of Flupirtin comes off by the combination of the above-mentioned effects. Thus for example, daa the opening of the central ATP dependent K+ channels was shown by SE antinociceptiv does not only work, but that it also the noradrenergen descending pain-modulating courses in back Marks activated (Narita, M, Takamori, K, Kawashima, N, Funada, M, Kamei, J, Suzuki, T, Misawa, M, Nagase, H. Activation OF cent ral ATP sensitive potassium channels produces the antinociception and spinal noradrenaline turnover enhancing effect into mice. Psychopharmacol.

113: 11-14,1993).

The damage mechanism of Flupirtin differs thereby clearly from that of the so-called peripheral analgesics such as Aspirin, Ibuprofen, Diclofenac, who unfold their analgetische effect over the inhibition of the Cyclooxygenase.

Since by Flupirtin the Prostaglandinsynthese is not restrained, also no damage of the gastrointestinal Schleimhaute takes place.

Also the renale function is not beeintrachtigt by Flupirtin . In chronic toxicological investigations (6-12 months) no referring to a liver-damaging effect were found.

Experimentally the analgetische effect of Flupirtin at awake dogs was examined.

Into anaesthesia the animals a silver wire was inserted and fixed into the Zahnpulpa (2nd molecular tooth). Subsequently, the animals were trained, in order to get accustomed to the personnel. One week after the Implantieren of the silver wire the animals were taken in attempt. The silver wire was connected with a surge generator, with whose assistance the Stromstäke could be adjusted steplessly.

Flupirtin was orally given to the dogs in a cap. 30 minutes later the amperage with kontinuerlicher Geschwindikeit was raised. With the first indication of the pain sensation the current generator was switched off immediately. The amperage, which was observed with the first indication of hurting, was considered as pain threshold. As indications symptoms were considered to the pain sensation such as salivation, leakage of the lips, twitching with the face musculature.

If Flupirtin were intravenously given, the measurement of the pain threshold 10 min took place after the substance gift.

The results are arranged in the table 1.

Table 1: SubstanzenID50inmg/kgnachID50inmg/kgnach of oral gift intravenous gift Flupirtin 3, 5 0, 7 Ibuprofen18 n.u. Diclofenac7,8 n. and Buprenorphin 1, 2 0.08 n. and: not examined regarding the analgetischen effect strength Flupirtin is clearly superior with dogs both ibuprofen and Diclofenac.

Buprenorphin is belonged a very strongly effective analgesic with a very small oral bio-availability and to the classical morphine derivatives.

Therefore it is not surprising that Buprenorphin worked after intravenous gift substantially more strongly analgetisch, as Flupirtin.

However the analgetische effect of Flupirtin was comparable after oral gift with by Buprenorphin.

It lets itself recapitulatory state that Flupirtin in dogs possesses a very strong analgetisches potential. Due to the damage mechanism and the available toxicological results a gastrointestinal is to expect renale or hepatische damage with more acute or application of long-terms not. Flupirtin can be given for pain treatment when degenerative illnesses with dogs and cats preferably orally, parenterally or rektal.

Suitable Darreichungsformen can be: Granulates, pellets, cap, micro caps, dragees, film tablet, chewing tablet, Retardtablette, two-layer tablets, Retardkapseln, Bolus, powders, Zäpfchen or Injektions-
 solutions.

Here formulations of tablet with simple or double break notch can be of advantage, in order to be able to applizieren the individually needed quantity the animals better .

For the acceptance increase of the oral Darreichungsformen for taste-better know dogs and cats, how Trigarol Digest P (hair man & Reimer GmbH) are added or artificial meat taste materials, for example consisting of vegetable protein and oil pig liver powder dried by soy beans and to portions between 5 10% to the tablet granulates.

With oral Darreichungsformen for example the single dosage can amount to for Flupirtin Maleat 0.1 to 20 mg/kg, preferably 1 to 5 mg/kg.

So can caps, which contain 100 mg Flupirtin Maleat two until are three times daily given.

The maximum daily dose should not exceed here 600 mg.

Suppositorien can contain as single dose 0.1 to 30 mg/kg, preferably 2.5 to 7.5 mg/kg Flupirtin Maleat. For example Zäpfchen with a dosage can be given by 100 to 300 mg Flupirtin Maleat two until three times daily.

The maximum daily dose should not amount to any more than 900 mg. Parenteral Darreichungsformen, preferably injection solutions for intra muscular application, contains preferably 1.5 to 5 mg/kg Flupirtin Gluconat (because of the better local compatibility).

For example ampuls with 164,5 mg Flupirtin Gluconat in 3 ml solution can be given once daily.

Examples Flupirtin tablet with double break notch: 10 kg of 2-Amino-3-carbethoxyamino-6 (4-fluor-benzylamino) - with 2,5 kg calcium hydraulic gene phosphate and 2.5 kg of corn strength pyridin mealeat are mixed and the mixture with a solution by 1 kg of Polyvinylpyrrolidon in 4 kg demineralized water in well-known way granulated. After adding 1,3 kg corn strength, 2 kg of micro-crystalline cellulose, 0.6 kg magnesium stearate and 0.1 kg hochdispersem silicon dioxide as well as 1.5 kg of taste-better Trigarol Digest P are pressed tablets with a weight by 200 mg, a diameter of 9 mm and a curvature radius by 10 mm with double break notch.

The breaking strength of the tablets amounts to 80 N to 100 N (Schleuniger break strengthening ester). The Zerfallzeit after DAB 8 amounts to 5 minutes.

Each tablet contains 100 mg active substance.

Flupirtin caps similar to the mode of production for tablets, described before, a cap filling is manufactured, which is filled up in hard gelatin capsules of the suitable size. Amount of filling per cap: 200 mg.

A cap contains 100 mg active substance.

Flupirtin Injektionslösung the manufacture course is valid for a beginning to 20 litres (= 6500 ampuls): Manufacture course : 1.10, 0 l water to 70°C are warmed up and left after addition of 1562,0 g Gluconsäure delta Lacton the solution one hour with 70°C.

The solution is begast thereby with nitrogen.

2. In solution 1 8000.0 g polyethylene glycol molecular weight 380 to 420 are weighed and the solution under nitrogen aeration is warmed up to 70°C.

3.30, 0 g Natriumdisulfit in 500.0 ml with nitrogen begastem water are drawn.

4. Solution 3 is given to solution 2.

5.666, 6 g Flupirtin base are gesiebt by a filter with the mesh size 0.3 mm and solved in solution 4 under intensive nitrogen aeration.

6. Solution 5 is filled up abgekühl) t and ad 20 litres with nitrogen begastem water.

7. Solution 6 is sterilely filtered by a membrane filter of the mesh size 0.2 lim with glass fiber prescreener.

8. Inprozesskontrolle : Measurement of the oxygen content of solution 7 by means of oxygen electrode. Measurement of the pH value of solution 7.

Solution 7 is filled up under aseptischen conditions as well as under nitrogen aeration into colorless ampuls, contents of 3 ml.

An ampul contains 164.5 mg Flupirtin Gluconat in 3 ml solution.

In accordance with the available invention Flupirtin or its can be used pharmaceutical usable salts also into combination with other active substances for pain treatment with degenerative joint illnesses by dogs and cats.

Here can the following combinations favourable-proves to be used: * Flupirtin in combination with Entzündungshemmern, in particular with selective COX-2-Hemmern, like Celecoxib, Rofecoxib, to reach Valdecoxib and Parecoxib around an effect exponentiation.

* Flupirtin in combination with other central effective analgesics such as Nefopam, Tramadol, Nalbuphin, Dextropropoxyphen * Flupirtin in combination with Metamizol * Flupirtin in combination with Chloroquin, Hydroxychloroquin, Methotrexat, Penicillamin, Ademetionin, Sulfasalazin, ß-Sitosterin, Thiamin, Cyano cobalamin, Pyridoxin * Flupirtin in combination with Steroiden, like Prednisolon, Methylprednisolon * Flupirtin in combination with the chondroprotektiven substances, like Chondroitin, Glukosamin and polysulfatiertes Glycosamingiykan * Flupirtin in combination with TNFa receptors * Flupirtin in combination with plant extracts, like devil claw root, Brennesselblätter, Guajakholz, pasture crust, Arnica